Melanotan I (Afamelanotide)

A Clinical Learning Guide for Medical Providers

MC1R-Selective α-MSH Analogue • Scenesse • Skin Resilience (1 of 2 Melanotans)

Evidence base at a glance: A skin-resilience peptide unlike the others in this group — it builds the skin's OWN photoprotection by driving pigment, and it is FDA-approved. Three facts dominate: (1) it is a highly MC1R-SELECTIVE α-MSH analogue — it stimulates eumelanin (UV-absorbing brown/black pigment) WITHOUT the sexual or appetite effects of Melanotan II (which hits MC3/4/5R too); (2) it is FDA- and EMA-APPROVED (Scenesse / afamelanotide) for erythropoietic protoporphyria (EPP) via a 16 mg subcutaneous implant — with strong Phase 3 data, an 8-year safety record, and NO melanoma signal in >1,000 patients; and (3) beyond pigment it has independent DNA-repair, antioxidant, anti-inflammatory, and even hepatoprotective actions. The widely used cosmetic-tanning version is OFF-LABEL, anecdotally SC-dosed, and — critically — the unregulated "melanotan" products are frequently mislabeled and contaminated. First of two Melanotan peptides (MT-II follows).

1. Peptide Profile

Name: Melanotan I / Afamelanotide (brand: SCENESSE, Clinuvel)

Classification: Synthetic, highly MC1R-selective melanocortin agonist; analogue of α-melanocyte-stimulating hormone (α-MSH)

Structure: Linear 13-amino-acid peptide — [Nle^4, D-Phe^7]-α-MSH (the substitutions give 10–1000× the potency of native α-MSH and resistance to breakdown)

Primary action: Stimulates eumelanin (brown/black, UV-protective pigment) synthesis in melanocytes — plus independent DNA-repair, antioxidant, and anti-inflammatory effects

FDA / EMA status: APPROVED — FDA Oct 2019 and EMA Dec 2014 — for erythropoietic protoporphyria (EPP) in adults (orphan drug, priority review). NOT approved for cosmetic use anywhere

Approved formulation: 16 mg biodegradable PLGA implant (1.7 cm rod), SC at the supra-iliac crest, every 2 months; max ~3–4 implants/year

Off-label use: Cosmetic tanning / photoprotection via empirical SC injection — investigational, unvalidated; unregulated products carry contamination and mislabeling risk

Where It Sits in the Skin Resilience Group

This is the third peptide in the Skin Resilience category and the first of the two Melanotans. It takes yet another distinct approach to skin resilience: GHK-Cu (guide 1) rebuilds the dermal matrix, Leuphasyl (guide 2) relaxes expression muscles, and Melanotan I strengthens the skin's intrinsic defense against UV by increasing protective pigment and supporting DNA repair. Where the first two are topical cosmetics, Melanotan I is, in its approved form, a genuine drug — the only EPP-approved melanocortin therapy — which gives it the most rigorous evidence base of any peptide in this category.

The Defining Distinction: MT-I vs MT-II (selectivity)

Melanotan I and Melanotan II are different peptides and must not be conflated (yet unregulated products routinely mislabel one as the other). Melanotan I is a LINEAR 13-aa peptide that is HIGHLY SELECTIVE for MC1R — so it drives pigmentation and photoprotection essentially without sexual or appetite effects. Melanotan II (the next guide) is a CYCLIC 7-aa peptide that NON-selectively activates MC1R, MC3R, MC4R, and MC5R — giving faster, more potent tanning but also the MC4R-mediated sexual and appetite/nausea effects. In short: MT-I is the selective, approved, "clean-tanning + photoprotection" peptide; MT-II is the broad, unapproved, more potent but more side-effect-laden one.

What EPP Is (and why pigment helps)

Erythropoietic protoporphyria is a disorder of heme synthesis in which protoporphyrin IX accumulates in tissue. Protoporphyrin IX is photoreactive: under visible light it generates oxidative stress, causing intense burning pain (without blistering) on sun exposure. By driving eumelanin — which absorbs UV and visible light and scavenges reactive oxygen species — Melanotan I increases the skin's tolerance to light and dramatically reduces phototoxic pain, which is the basis of its approval.

2. Modes of Action & Mechanisms

Melanotan I binds MC1R on melanocytes and triggers a cAMP cascade that does far more than tan the skin: downstream of cAMP the signal splits into independent arms — pigmentation, DNA repair, antioxidant defense, and anti-inflammation — which together explain both its cosmetic and its therapeutic effects.

MC1R → cAMP → MITF: The Pigmentation Cascade

- **MC1R binding:** afamelanotide binds MC1R on melanocytes with 10–1000× the potency of native α-MSH
- **cAMP → PKA → CREB:** Gs-protein activates adenylyl cyclase, raising cAMP; PKA then phosphorylates CREB (Ser133)
- **MITF induction:** CREB drives MITF (microphthalmia transcription factor) — the master regulator of melanocyte function
- **Eumelanin synthesis:** MITF upregulates tyrosinase, TRP-1, TRP-2 → brown/black eumelanin, which absorbs UV/visible light and scavenges ROS

Beyond Pigment: Dual Independent cAMP Pathways

A key insight is that MC1R's effects diverge below cAMP into independent arms: the PIGMENTATION arm (PKA→CREB→MITF) and a separate DNA-REPAIR arm (PKA→ATR/ATM phosphorylation→nucleotide excision repair). These operate independently — NER is MITF-independent and eumelanin synthesis is ATR-independent — so Melanotan I can support genome integrity against UV damage over and above simply darkening the skin.

Four Functional Arms

Arm	Key Mediator	Function
Pigmentation	MITF	Eumelanin synthesis (UV/visible-light absorption, ROS scavenging)
DNA repair	ATR/ATM → NER & BER	Nucleotide- and base-excision repair; p53 stabilization; ↓ thymine dimers and oxidized bases
Antioxidant	Nrf2	Rescues UV-induced Nrf2 downregulation; ↑ HMOX1, GCLC, GSTP1 — ROS scavenging
Anti-inflammatory	NF-κB inhibition	Blocks IκBα degradation; ↓ TNF-α, IFN-γ, IL-1β, IL-6; ↑ IL-10; ↓ adhesion molecules

DNA Repair (the therapeutic frontier)

Afamelanotide supports DNA repair through several activities: phosphorylating ATR/ATM via PKA, activating NER factors (XPC, XPB, XPD), stabilizing p53, engaging the base-excision-repair pathway (p21/GADD45, OGG1, APE1), and reducing oxidation of purine/pyrimidine bases. The CUV156 study provided first clinical confirmation that afamelanotide assists DNA repair in xeroderma pigmentosum (XPC) patients — those with the most severe repair deficiency — pointing toward uses well beyond tanning.

Mechanistic takeaway: Melanotan I doesn't just tan — it activates the skin's full UV-defense program. One MC1R signal branches into pigment (eumelanin), DNA repair (NER/BER), antioxidant rescue (Nrf2), and anti-inflammation (NF-κB). Its MC1R selectivity means it does this WITHOUT the MC4R-driven sexual/appetite effects of Melanotan II.

3. Points of Clinical Relevance

1. It is FDA-approved — but only for EPP, and only as the implant

For erythropoietic protoporphyria, Melanotan I (Scenesse) is approved medicine with strong Phase 3 data and a multi-year safety record — a different footing from research peptides. That approval is narrow: it covers the 16 mg implant for adult EPP only. Cosmetic tanning, vitiligo, and every other use are off-label or investigational.

2. MC1R selectivity is the whole point — "clean" pigmentation without MT-II's effects

Because Melanotan I is highly MC1R-selective, it drives tanning and photoprotection without activating MC4R — so, unlike Melanotan II, it produces no sexual effects, no appetite suppression, and a milder side-effect profile (mainly nausea and implant-site reactions). For patients who want photoprotection or tanning without the broader melanocortin effects, MT-I is the cleaner choice.

3. Its value extends past tanning — DNA repair, anti-inflammation, hepatoprotection

The independent DNA-repair arm (confirmed clinically in XP patients), the antioxidant/anti-inflammatory effects, and a dose-dependent hepatoprotective effect in EPP (falling ALT, AST, bilirubin, and protoporphyrin IX) make Melanotan I more than a tanning agent.

These broaden its rationale toward photodermatoses and tissue protection — though most non-EPP uses remain investigational.

4. Genuine photoprotection — but it does NOT replace sunscreen or sun avoidance

The evidence for photoprotection is real: fewer sunburn cells, reduced thymine-dimer formation, increased melanin density, and effective pigmentation even in people with MC1R variant alleles (those who tan poorly and most need protection). Even so, the EPP label REQUIRES continued sun protection during treatment — the pigment raises tolerance, it does not make the skin UV-proof.

5. Cosmetic SC dosing is off-label, unvalidated, and a sourcing minefield

The empirical cosmetic protocol the lecturer describes — roughly 250–500 µg SC daily with sun exposure for the first ~7–10 days, then ~twice weekly to maintain, or a 7-day pre-vacation load — is anecdotal, non-standardized, and unsupported by RCTs. More importantly, unregulated "melanotan" products lack GMP controls, are frequently MISLABELED (MT-I sold as MT-II and vice versa), and carry documented contamination risk; Australia issued a formal safety warning. If used at all, it must be genuine, with informed consent.

6. Mandatory skin surveillance — because it changes pigment and nevi

Because Melanotan I drives melanocyte activity, twice-yearly full-body skin examination with dermoscopy is mandatory, with documentation and monitoring of all nevi for morphologic change. Reassuringly, long-term data (1,023 implants in 115 patients over 8 years; 323 patients up to 10 years) show NO melanoma signal — but melanoma history and premalignant lesions are contraindications, and surveillance is non-negotiable.

4. General Dosing & Delivery Options

FDA/EMA-approved dosing exists for EPP (the implant, below). Cosmetic SC dosing is OFF-LABEL, empirical, non-standardized, and unsupported by trials — and unregulated product is a contamination/mislabeling hazard. For educational context only.

FDA/EMA-Approved Protocol (EPP)

Parameter	Detail
Dose / form	16 mg biodegradable PLGA implant (1.7 cm rod)
Route	Subcutaneous, anterior supra-iliac crest (trained provider, 14-gauge cannula)
Frequency	Every 2 months; ~3 implants/year seasonally (spring–autumn); EMA max 4/year
PK	Tmax ~36 h; >90% released by day 5; below detection by ~day 10; implant half-life ~15 h (free peptide ~30 min)
Monitoring	Full-body skin exam twice yearly; maintain sun protection throughout

Off-Label Cosmetic / Photoprotection Dosing (anecdotal — not validated)

- **Loading:** ~250–500 µg SC daily with sun/UV exposure for the first ~7–10 days to build pigment
- **Maintenance:** ~twice weekly thereafter to maintain the pigment response (highly variable between individuals)
- **Pre-exposure protocol:** start ~7 days before anticipated sun exposure, continue through, then drop to ~twice weekly
- **Reality check:** no standardized regimen, no long-term data, no RCTs — entirely anecdotal; document route, dose, and response if used

Synergies & Combinations

- **MT-I + UV-B / sunlight:** Phase I confirmed synergistic tanning — equivalent tan with ~50% less UV; tan maintained ~3 weeks longer
- **MT-I + NB-UVB (vitiligo):** combination promotes melanoblast differentiation/proliferation and repigmentation (investigational)
- **MT-I + PDE4 inhibitors (theoretical):** may enhance MC1R signaling by preventing cAMP degradation — mechanistic only

5. Evidence Profile

Evidence tier distribution: the STRONGEST in the Skin Resilience group — multiple Phase 3 RCTs in EPP, a vitiligo RCT, mechanistic and photoprotection studies, and long-term observational safety (up to 10 years). The caveat: nearly all rigorous data are for the APPROVED implant in EPP; cosmetic SC tanning use has no controlled evidence.

EPP — Phase 3 RCTs (the approval basis)

Trial	N	Key Outcome
CUV017 (crossover, 12 mo)	91	Reduced pain days (p=0.0023); melanin density +28–29%
CUV029 (parallel, 9 mo)	74	Up to 7× longer sun exposure; 50% fewer phototoxic reactions; pain 6.0 vs 17.5
CUV030 (parallel, 6 mo)	77	Improved sun tolerance (p=0.036); QoL (p<0.001)
CUV039 (US, parallel, 6 mo)	94	~70% more pain-free sun hours (69.4 vs 40.8 h, p=0.04)

Other Indications (investigational)

- Vitiligo RCT (Lim 2015, n=55): afamelanotide + NB-UVB gave 48.6% vs 33.3% repigmentation and faster onset vs NB-UVB alone (p<0.05)
- PMLE (Phase 3): reduced rash severity; solar urticaria (Phase 2, n=5): higher melanin density and urticarial threshold; acne (open-label, n=3): fewer inflammatory lesions
- Xeroderma pigmentosum (CUV156): first clinical confirmation of assisted DNA repair in XPC patients

Photoprotection & Hepatoprotection

- Photoprotection: 47% fewer sunburn cells; reduced thymine dimers (65 subjects); pigmentation even with MC1R variant alleles
- Hepatoprotection (EPP, n=70; dose-dependent): ↓ ALT (p=0.012), ↓ bilirubin (p=0.030), ↓ AST (p=0.015), ↓ protoporphyrin IX (p<0.0001) — via MC4R-mediated anti-inflammatory action on hepatic stellate/Kupffer cells

Long-Term Safety

- Biolcati 2015: 115 EPP patients, 1,023 implants over up to 8 years (314 patient-years) — only minor AEs; NO melanoma; EMA PASS: 323 patients up to 10 years, no new concerns

Critical gaps: Rigorous evidence is concentrated in APPROVED EPP use — cosmetic SC tanning has NO RCTs, no standardized dosing, and no long-term safety data, and unregulated product is frequently mislabeled/contaminated. Most non-EPP indications (vitiligo, PMLE, solar urticaria, acne, XP) remain investigational. No formal drug-interaction studies. The reassuring no-melanoma record is from a monitored EPP population, not from unsupervised cosmetic users.

6. Clinical Considerations

Contraindications

- **Melanoma history / dysplastic nevus syndrome:** contraindicated
- **Current premalignant or malignant skin lesions** (Bowen disease, BCC, SCC): contraindicated
- **Hypersensitivity** to afamelanotide or the PLGA polymer
- **Pregnancy, lactation, age <18:** contraindicated
- **Severe hepatic or renal impairment:** contraindicated (insufficient PK data)

Drug Interactions

No formal drug-interaction studies have been conducted. Use clinical judgment, particularly with photosensitizing agents and other melanocortin-active compounds. Document all concurrent medications.

Monitoring Parameters

Parameter	Frequency	Rationale
Full-body skin exam + dermoscopy	Twice yearly (mandatory)	Pigment/nevi changes; melanoma surveillance
Nevi documentation/photography	Baseline + ongoing	Detect morphologic change
Sun protection adherence	Throughout treatment	EPP requirement; pigment is not UV-proof
Liver markers (EPP)	Periodic	Hepatoprotective monitoring (ALT/AST/bilirubin/PPIX)

Cadence: baseline full-body skin exam with dermoscopy and nevus documentation; for approved EPP use, implant every 2 months seasonally with twice-yearly skin exams and continued sun protection; monitor liver markers where relevant. For any off-label cosmetic use, verify genuine product, obtain informed consent, and document dose/route/response. Discontinue for any new or changing pigmented lesion.

Safety Profile

- Phase 3: mostly mild/moderate AEs — implant-site reaction (~21%), nausea (~19%), oropharyngeal pain, cough, fatigue, hyperpigmentation (~4%); no serious safety concerns
- Long-term: no melanoma signal across 8–10-year datasets in monitored EPP patients; high compliance
- Unregulated cosmetic product: contamination and mislabeling are the principal real-world hazards (Australian safety warning, 2025)

Regulatory Status

Melanotan I / afamelanotide (Scenesse) is FDA-approved (Oct 2019) and EMA-approved (Dec 2014) for EPP in adults. It is NOT approved for cosmetic tanning anywhere; cosmetic SC use is off-label/investigational, and unregulated "melanotan" products are not GMP-controlled and are frequently mislabeled (often confused with Melanotan II). Any non-EPP use requires documented informed consent.

7. Final Note

As the third peptide in the Skin Resilience group and the first of the two Melanotans, Melanotan I offers a distinctive strategy: rather than rebuilding the matrix (GHK-Cu) or relaxing muscle (Leuphasyl), it strengthens the skin's intrinsic UV defense — driving protective eumelanin while independently supporting DNA repair, antioxidant rescue, and anti-inflammation. Its MC1R selectivity is the defining feature: it delivers pigmentation and photoprotection without the sexual or appetite effects that come with Melanotan II's broader receptor activity. And uniquely in this category, its approved form is a real, well-studied drug — Scenesse for EPP — with Phase 3 efficacy, an 8-to-10-year safety record, and no melanoma signal.

The honest framing is a sharp split between the approved and the off-label. For EPP, the evidence is robust and the benefit (up to 7× longer pain-free sun exposure, better quality of life, even hepatoprotection) is clinically meaningful. For cosmetic tanning — the way most people encounter "melanotan" — the picture is the opposite: no RCTs, no standardized dosing, no long-term safety data in that population, and a genuine sourcing hazard, since unregulated products are frequently mislabeled (MT-I vs MT-II) and contaminated, prompting formal safety warnings. The reassuring melanoma data come from monitored EPP patients, not unsupervised cosmetic users.

For the clinician, Melanotan I is best understood as two things at once: an approved orphan-disease therapy with excellent evidence, and an off-label cosmetic peptide whose appeal (a protective tan, photoprotection for those who burn) is real but whose use demands genuine product, informed consent, mandatory skin surveillance, and continued sun protection. The next guide covers Melanotan II — the broader, more potent, unapproved counterpart — where the trade-offs shift markedly toward stronger effects and more side effects.

Bottom line: An MC1R-SELECTIVE α-MSH analogue and the first of two Melanotans — it builds the skin's own UV defense (eumelanin + DNA repair + antioxidant + anti-inflammatory) WITHOUT MT-II's sexual/appetite effects. FDA/EMA-APPROVED (Scenesse) for EPP via 16 mg implant, with strong Phase 3 data, 8–10-year safety, no melanoma signal, and dose-dependent hepatoprotection. Cosmetic tanning use (empirical SC, ~250–500 µg) is OFF-LABEL, unvalidated, and a contamination/mislabeling hazard. Mandatory twice-yearly skin exams; sun protection still required. Approved for EPP; off-label otherwise. MT-II follows.

Selected References

1. FDA. SCENESSE (afamelanotide) Prescribing Information. NDA 210797. Oct 2019.
2. EMA. SCENESSE EPAR / SmPC. EMA/H/C/002548. Dec 2014.
3. Böhm M et al. Benefits and risks of chronic MC1R activation. JEADV. 2024. [Review]
4. Garcia-Borrón JC et al. MC1R, the cAMP pathway, and the response to solar UV. Pigment Cell Melanoma Res. 2014. [Review]
5. Jarrett SG et al. Divergence of cAMP pathways: nucleotide-excision repair and melanogenesis. Exp Dermatol. 2017. [In Vitro]
6. Langendonk JG et al. Afamelanotide for erythropoietic protoporphyria (CUV029/CUV039 Phase III). [Clinical Trial]
7. Lim HW et al. Afamelanotide and narrowband UV-B phototherapy for vitiligo. JAMA Dermatol. 2015;151(1):42–50. [Clinical Trial]
8. Dorr RT et al. Evaluation of a superpotent melanotropic peptide with UV-B (photoprotection). Arch Dermatol. 2004;140(7):827–835. [Clinical Trial]
9. Barnetson RS et al. [Nle4-D-Phe7]-α-MSH increases melanin in MC1R-variant individuals (Phase II). 2006. [Clinical Trial]
10. Biolcati G et al. Long-term observational safety of afamelanotide in EPP (8 years). Br J Dermatol. 2015;172(6):1601. [Observational]
11. Balwani M et al. Dose-dependent liver protection with afamelanotide in EPP. Life. 2023. [Clinical Trial / Observational]
12. Clinuvel Technical Note. CUV156: assisted DNA repair in XPC patients. 2023. [Clinical Trial]
13. Catania A et al. Anti-inflammatory effects of α-MSH / melanocortins. [Reviews]
14. FDA Multi-Discipline Review NDA 210797 (PASS data: 323 patients, up to 10 years). [Regulatory]

For educational and research purposes only. Not medical advice. Melanotan I / afamelanotide (Scenesse) is FDA- and EMA-approved ONLY for erythropoietic protoporphyria (EPP) in adults; cosmetic tanning and all other uses are off-label/investigational. Unregulated "melanotan" products are not GMP-controlled and are frequently mislabeled (commonly confused with Melanotan II) and contaminated — a documented safety hazard. Mandatory twice-yearly skin surveillance applies; melanoma history and premalignant lesions are contraindications. First of two Melanotan peptides in the Skin Resilience series. Based on lecture materials by William Seeds, MD — SSRP Institute | Cellular Medicine Education.